MicroManagers

microRNA: Small molecules with big potential in stem cell research

by Courtney Humphries

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Robert Blelloch, a stem cell biologist at the University of California San Francisco, has been trying to understand how a cell hangs ontoits identity over time.

Here's the dilemma: Each cell in your body shares the same DNA with every other cell. So how does a heart muscle cell know to contract rhythmically, while an immune cell recognizes and attacks foreign invaders and groups of neurons form complex networks in the brain? Then, if our neurons and our heart cells share the same DNA, why don't neurons start beating? Or grow hair?

These questions are more than a dusty academic curiosity. The answers could mean new therapies for diseases like diabetes, spinal cord injury, HIV/AIDS and neurodegenerative diseases or better ways of reprogramming adult cells into therapeutically useful embryonic-like stem cells.

Now, Blelloch and other scientists are getting excited about a relative newcomer to biology: tiny molecules called microRNAs that seem to have a major role in directing cells from one identity to another and in holding cells in their eventual fate. They may in part explain how two cells with identical DNA could become neurons or heart muscle and why those neurons don't beat. "People believe they could be very powerful molecules that we can get a handle on and use to manipulate cells," Blelloch says.

With such a seemingly broad role in controlling a cell's fate, microRNAs may represent a new opportunity to understand stem cells and control them in laboratory research and experimental therapies. This potential isn't lost on stem cell researchers in California and around the world. In 2009, CIRM grantees alone have published eleven papers linking microRNAs to stem cell biology. If Blelloch and others are right, microRNAs could be both a tool for understanding the basic biology of stem cells and for developing future therapies. (See "The Cancer Connection" below.)

Guiding Development

Different cell types may share the same DNA, but they use that DNA differently. Certain genes are more active in a skin cell than they are in a muscle cell, while other genes may be completely inactive. This basic fact has been known for decades. What wasn't entirely clear is what controlled those genetic decisions.

MicroRNAs were first discovered in the early 1990s in worms but it wasn't until the early 2000s that scientists began to appreciate their larger importance in mammals. In a cell, RNA was thought to do one of two things: carry a protein-coding message from the nucleus or help the cell translate that RNA message into a new protein. RNA molecules were essentially thought of as go-betweens in the process of turning genes into proteins, not regulators of the cell's normal activities. But scientists discovered that microRNAs actually control which genes produce proteins, thereby shaping the fate of the cell. This unexpected finding shook up biology. (See "Understanding RNA" below.)

"It essentially represents a whole new layer of how the genetic code is interpreted by a cell," says Deepak Srivastava, director of the Gladstone Institute of Cardiovascular Disease, who has received a CIRM grant to study microRNAs. The Gladstone Institutes, located in the budding biotech community of Mission Bay in southern San Francisco, is affiliated with the University of California, San Francisco.

Srivastava has been studying the role microRNAs play in the normal development of the heart. He has uncovered specific microRNAs that can lead embryonic stem cells to become three different kinds of cells of the cardiovascular system. Getting stem cells to differentiate into a cell type of choice is one of the most difficult problems facing stem cell researchers. In his practice, Srivastava cares for children with heart defects that are a direct result of failure of cardiac stem cells to properly differentiate. He hopes his discovery can help make sense of these diseases and eventually find ways to use stem cells to create heart tissue to treat cardiac defects in

children and also restore cardiac function in adults.

Holding Stem Cells in Check

While some microRNAs guide cells down a particular developmental path, others seem to hold stem cells as stem cells. In keeping with that, Jeanne Loring at The Scripps Research Institute near San Diego has shown that embryonic stem cells have a different pattern of microRNAs than are present in other cell types. She suggests that the work, which was funded by CIRM, could lead to better ways of both maintaining and deriving stem cell lines.

Up in San Francisco, Blelloch's lab has found that a set of these stem cell-specific microRNAs are critical for an important property of stem cells: their ability to make new copies of themselves, known as self-renewal. This discovery has implications for scientists' ability to create induced pluripotent stem cells—adult cells that are reprogrammed to act like embryonic stem cells. The standard method of creating these cells is to insert genes into the DNA of an adult cell such as skin. According to Blelloch's research published early in 2009 and funded by CIRM, introducing microRNAs into a cell could be an alternative way of transforming cells, one that is safer, more efficient, and does not rely on modifying the cells genetically. (See the video at left "Genetic Molecule Enables Safer Method For Creating iPS Cells")

At the University of California, Santa Barbara, Ken Kosik's laboratory described another microRNA involved in maintaining a property of stem cells: the ability of embryonic stem cells to give rise to all other types of cells, known as pluripotency. Na Xu, a postdoctoral fellow in his lab supported by a CIRM training grant, found that this microRNA dampens the activity of three key genes that are critical for pluripotency. When levels of this microRNA are high, the cell begins to differentiate. But blocking the molecule can prevent cells from differentiating and maintain them in a pluripotent state.

It turns out that the microRNA under investigation in Kosik's lab, called miR-145, is one of the group discovered by Deepak Srivastava to promote cardiovascular system differentiation. In Kosik's lab, inhibiting this microRNA helps maintain the stem cell as a stem cell, while Srivastava hopes to harness that microRNA's ability to push the cells down the path toward heart cells.

A Practical Solution

One reason scientists are excited about microRNAs is their practicality. It may be relatively easy to introduce these small molecules into cells, in contrast to trying to manipulate the genes in a cell directly using viruses.

"They can potentially someday be delivered like a drug," Blelloch says. MicroRNAs are only active for a period of time, so they behave more like drugs and don't require making permanent changes to a cell's DNA. Yet one or two of these powerful molecules may be enough to make a dramatic impact on a cell's state.

In fact, Blelloch says it may be possible someday to use them to drive stem cell processes within the body without the need for introducing new cells: for instance, giving microRNA to a patient with a damaged liver to temporarily activate stem cells in the organ. But using microRNAs as therapies will require more knowledge about how they work, and the quest to understand them is just beginning.
